IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

IN RE APPLICATION OF: Nandan P. Koppiker, et al.

APPLICATION NO.: 10/731,905 : Examiner: Raymond J. Henley III

FILING DATE: **December 10, 2003** : Group Art Unit: **1614**

TITLE: TREATMENT OF NEUROPATHY

Commissioner for Patents
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Dear Sir:

BRIEF ON APPEAL

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Appellants appeal the Final Office Action mailed April 10, 2006 which finally rejected claims 17-34. A Notice of Appeal was filed on June 16, 2006 and was marked as received by the U.S.P.T.O. on June 19, 2006. Accordingly, a timely petition for a two month extension of time and fee transmittal are filed herewith.

This Brief contains items identified in the Table of Contents below under the headings as required by 37 C.F.R. 1.192

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REAL PARTY IN INTEREST

This Application is assigned to Pfizer Inc., a U.S. Corporation organized under the laws of the State of Delaware and having its headquarters at 235 East 42nd Street, New York, New York USA.

RELATED INTERFERENCES AND APPEALS

The subject matter of this Appeal is not related to any co-pending Interferences or Appeals in the U.S. Patent & Trademark Office.

STATUS OF CLAIMS

1. Claims cancelled: 1-16.
2. Claims withdrawn from consideration but not cancelled: none
3. Claims pending: 17-34 have been rejected under 35 USC §103(a) in the final Office Action mailed April 10, 2006.
4. No claims have been allowed.

STATUS OF AMENDMENTS

All amendments have been entered without objection.

SUMMARY OF THE INVENTION

Appellants' independent claim 17 is directed to a combination comprising a therapeutically effective amount of a cGMP inhibitor and a therapeutically effective amount of pregabalin or gabapentin (Specification page 11, line 34- page 12, line 16). Further Appellants' independent claim 18 is directed to a single composition (the three ingredients: the cGMP inhibitor, pregabalin or gabapentin and a excipient, diluent or carrier are together in a single dosage form, e.g., in the form of a tablet, capsule or suspension) (Specification page 9, lines 1-4; page 11, line 34- page 12, line 16). Appellants discovered that the cGMP inhibitor and pregabalin or gabapentin, if used together optionally in combination with a excipient, diluent or carrier provide a significant medical benefit.

Independent claim 27 is directed to a method of treating neuropathy in a patient suffering therefrom that comprises administering a patient a therapeutically effective amount of

a combination of a cGMP inhibitor and pregabalin or gabapentin (Specification page 1, lines 1-4; page 11, line 34- page 12, line 16).

A preferred cGMP inhibitor is sildenafil or pharmaceutically acceptable salts thereof for the pharmaceutical composition (claim 21) and the method of treatment (claim 32) .(Specification page 6, lines 14-17; page 8, lines 34-35; e.g., claim 26).

Appellants recognize that cGMP inhibitors (e.g., sildenafil) and pregabalin and gabapentin were individually known *per se* and, that when used alone, each agent could be administered to treat certain medical conditions. However, what was not known or described in the cited references, was the use of the specific agents in combination, optionally together in a single composition, preferably for the treatment of neuropathy.

GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

I. Claims 17-34 stand rejected under 35 USC §103(a) over Yamasaki et al. (U.S. Patent No. 6,166,219) in view of Ellis et al. (WO 94/28902), Singh (WO 98/03167), Bueno et al. (U.S. Patent No. 6,127,418) and Stedman's Medical Dictionary (Twenty-Second Edition; 1972).

ARGUMENTS

A. THE EXAMINER'S REJECTION OF CLAIMS 17-34 UNDER 35 U.S.C. §103(a).

The Final Rejection (page 2 incorporates by reference the earlier September 8, 2005 rejection which follows) states that Yamasaki et al. teaches a pharmaceutical composition comprising a cGMP inhibiting benzimidazole compound of the formula (I) (col. 35, line 64-col.36, line 26) in combination with a pharmaceutically acceptable carrier (col. 37, line 65-col. 38, line 6) and further teaches a method of treating a disorder that is responsive to treatment with a cGMP PDE inhibiting compound of formula (I) (col. 35, lines 22-55). The Final Rejection also states that the disclosed composition can be administered orally in the solid form of tablets, granules, powders or capsules or in liquid forms, such as solutions, suspensions, syrups, emulsions or lemonades (col. 37, line 65-col.38, line 9). The Final Rejection also states that Yamasaki et al. further teaches diabetic neuropathy as a medical condition responsive to treatment with the cGMP inhibiting compounds (col. 1, lines 14-44, especially line 21).

The Final Rejection admits that the Yamasaki et al. reference does not teach the concomitant administration of gabapentin or pregabalin with a cGMP inhibitor or a formulation of gabapentin or pregabalin in combination with a cGMP inhibitor in a pharmaceutical composition (see present claims 17, 18, 22, 23, 27, 33 and 34);

The Final Rejection, however, states that the claims would have been obvious because both gabapentin and pregabalin were well known in the art to be useful for the same therapeutic purpose of treating diabetic neuropathy. (Singh WO 98/03167 (page 5, lines 9-19 and page 7, lines 4-20) and Bueno et al., U.S. Patent No. 6,127,418, (col. 2, lines 50-55)). The Final Rejection states that it would, therefore, have been obvious to employ either gabapentin or pregabalin in combination with a cGMP inhibiting composition, as disclosed by Yamasaki et al., because each compound was known in the art to be successful for achieving the same therapeutic effect. The Final Rejection states that motivation to administer both compounds flows logically from the efficacy of each compound in treating diabetic neuropathy in the absence of evidence to the contrary, and it is generally *prima faci* obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA) and MPEP §2144.06.

The Final Rejection admits that the Yamasaki et al. reference does not teach the particular use of sildenafil as the cGMP inhibitor (see present claims 21 and 32). But the Final Rejection states that Yamasaki et al. discloses that diabetic neuropathy is a condition responsive to treatment with a cGMP PDE (particularly a cGMP PDE5) inhibiting compound. The rejection states that in light of such a relationship, it would have been an obvious conclusion that the treatment of a condition known to be responsive to a cGMP PDE5 inhibiting agent would not be solely limited to those compounds disclosed by Yamasaki et al.. Instead, according to the Examiner, one would reasonably expect that any cGMP inhibitor compound, such as sildenafil or a pharmaceutical composition thereof, would effectively treat such a condition.

The rejection states that Ellis et al. teaches the compound 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (otherwise known as sildenafil) as a potent and selective inhibitor of cGMP-specific PDE5 (page 7, lines 1-3 and page 9, lines 1-3 of the last paragraph).

Further specific comments made by the Examiner in the Final Rejection are incorporated into and specifically replied to in the text below for the convenience of the Board.

B. INTRODUCTION TO APPELLANTS ARGUMENTS

Appellants traverse the Final Rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Yamasaki et al. in view of Ellis et al., Singh, Bueno et al. and Stedman's Medical Dictionary.

Appellants submit that the threshold issue is whether the Examiner has carried the burden to establish *prima facie* obviousness from the cited references -- is there something in the art that motivates a skilled worker to combine the claimed materials, coupled with a reasonable expectation that if this were done, a beneficial result would be obtained? Appellants respectfully submit that the answer is "no", and therefore no case of *prima facie* obviousness has been established.

In addition, Appellants separately submit that there is nothing to motivate the particular selection of sildenafil (or its pharmaceutically acceptable salts) among cGMP inhibitors.

Accordingly, Appellants respectfully request that this application be passed to issue.

C. THE EXAMINER MADE FOUR PRIMARY ERRORS

Appellants submit that the Examiner's rejection is flawed in at least the four critical respects discussed below.

First, the Examiner appears to be stating that the Yamasaki et al. benzimidazole compounds are cGMP PDE5 inhibitors and that they are stated to be useful for the treatment of diabetic neuropathy, and accordingly, all cGMP PDE5 inhibitors are useful for the treatment of diabetic neuropathy. Yet, it is clear that the treatment of diabetic neuropathy by the benzimidazole compounds could be mediated by some other listed mechanism of action(s) (e.g., smooth muscle cell suppressing activity or yet another cGMP PDE isoform). Thus, Yamasaki et al. never directly links the two i.e., cGMP PDE5 inhibition and diabetic neuropathy. While Yamasaki et al. discloses cGMP PDE5 and separately diabetic neuropathy, any connection between the two is confounded by other confusing and/or conflicting Yamasaki et al. statements (see e.g., col. 35, line 35-36; col. 164, lines 65-67-col.165, lines 1-26) that in combination create a level of grammar and scientific confusion as to what the reference discloses.

Second, the gap in Yamasaki et al.'s teachings cannot be bridged by the Examiner's reliance on anticipation law (which is not appropriate in an obviousness determination). Both the MPEP § 2131.02 and *Ex parte A* address anticipation and not obviousness. The Examiner improperly relied on *Ex Parte A* in an obviousness context to motivate a specific selection of one disease/condition from among many. The holding of *Ex Parte A* is not applicable to this obviousness rejection.

The third error is that the rejection is contrary to the law of obviousness. A *prima facie* case of obviousness requires both motivation to combine and reasonable expectation of success. "obvious to try" is not sufficient. The Yamasaki et al. passages relied on by the Examiner are simply a classic invitation to experiment to determine which disease/condition should be linked with a particular mechanism of action. At best, this is an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988)

Fourth, the Examiner erroneously refuted Appellants' March 6, 2006 Response, stating that: "two or more compounds, used together, may have different mechanisms of action [resulting in a drug-drug interaction] is not a very impressive argument against such use because if this were true, than it would have to be the case that no two or more drugs could be used in combination with each other unless they each possessed the same mechanism of action." (Final Rejection page 8) This conclusion is simply incorrect. It is true that such drug combinations may have drug-drug interactions, and it is the unpredictability of such drug-drug interactions that is an important aspect of the lack of a reasonable expectation of success of Appellants drug combination. In addition, the confusing nature of the contradictory Yamasaki et al. statements raises a sufficient doubt as to the reasonable likelihood of success.

Simply stated, at least these four basic underpinnings of the Examiner were erroneous, and without them, there is no support for the Examiner's obviousness conclusion. There is nothing in Yamasaki et al. (or the other cited art) that motivated one skilled in the art to select diabetic neuropathy from among the many disease/conditions listed or to select the cGMP PDE5 mechanism. There is clearly nothing to directly link the selected diabetic neuropathy with the selected cGMP PDE5 mechanism. Further still, there is nothing to suggest the combination of the selected cGMP PDE5 inhibitor with the further selected specific gabapentin or pregabalin since they have different mechanisms of action, or were that combination made, that there would be a reasonable expectation of success. At least all of these selection and combination steps must occur for there to be a *prima facie* case of obviousness and the quality and quantity of selection and combination steps presents a clear case of the impermissible use of hindsight. Further still, Appellants have raised a sufficient doubt as to the reasonable expectation of success, at least because of the confusion due to the conflicting Yamasaki et al. statements and as a result of the possible drug-drug interactions. Thus, the Examiner's rejection is flawed in at least these four critical respects and others all of which are further described below.

D. YAMASAKI ET AL. DOES NOT STATE THAT DIABETIC NEUROPATHY MAY BE TREATED BASED ON CGMP PDE5 ACTIVITY.

Appellants submit that there are four separate distinct passages (only some of which were relied upon by the Examiner) in the Yamasaki et al. specification that are related to diabetic neuropathy and Appellants have reviewed the passages with regard to their

relationship to inhibitors. These quotations are not merely the self-serving arguments of an Applicant seeking to refute the Examiner's contention, these are the express words of Yamasaki et al., and they remove the key underpinnings of the Examiner's rejections and underscore that further research is needed. Nothing but hindsight allows one to pluck the specific disease/condition and combine it with a particular mechanism to reconstruct part of the instant claims. Appellants submit that these four passages taken as a whole lack a clarity of description and science that results in confusion regarding what is disclosed. Further the reference actually suggests in some passages the opposite (diabetic neuropathy treated by blood sugar lowering activity) of that stated by the Examiner. In addition, this confusion clearly raises a sufficient doubt regarding the reasonable expectation of success. For clarity and completeness, Appellants provide the following descriptions of each passage since it is axiomatic that one cannot pick and choose only certain passages from a reference (the art must be taken as a whole).

But first, Appellants provide some information well known to those skilled in the art as scientific background. A compound may interact with many different enzyme targets resulting in the compound having several different mechanisms of action. In turn each of those interactions may result in mediating one or more specific enzyme pathways and the mediation of each enzyme pathway may impact a disease(s)/condition(s). Accordingly, if a compound interacts with several different enzyme targets (it is nonspecific) it could be known as a X inhibitor and also a Y inhibitor. As a result of the inhibition of X and Y the compound may potentially impact several diseases. However, it is critical to understand that some of those diseases are impacted as a result of the inhibition of X and some of those diseases are impacted as a result of the inhibition of Y. Restated a disease is impacted by intervention with a specific enzyme and not all the diseases treated by a compound are a result of inhibition of each and every enzyme that the compound inhibits. The fact that a compound that is an inhibitor of a particular enzyme may treat a disease, but not as a result of interaction with that enzyme, reinforces Appellants arguments. With this as Background Appellants turn to the four specific Yamasaki et al. passages.

Specifically, in the first passage, col. 1, lines 14-44 certain benzimidazole derivatives are suggested for preventing and treating a plethora of about five dozen disease/conditions. While one of the disease/conditions listed is diabetic neuropathy there is quite simply no motivation

from this passage to utilize a cGMP-PDE5 inhibitor for the treatment of diabetic neuropathy. The passage simply does not mention the cGMP-PDE5 mechanism of action. Neither does the Examiner provide any reasoning that provides the motivation to modify the first passage (col. 1, lines 14-44) from a disclosure of a multitude of uses (including diabetic neuropathy) for certain benzimidazole derivatives to a disclosure of the use of certain inhibitors for the treatment of diabetic neuropathy.

In the second passage (col. 35, lines 22-36) certain benzimidazole derivatives are suggested for preventing and treating about two dozen disease/conditions "based on their blood sugar level-depressing activity". While one of the disease/conditions listed is diabetic neuropathy, there is quite simply insufficient motivation from this passage to utilize a cGMP-PDE5 inhibitor (i.e., a cGMP PDE5 mechanism) for the treatment of diabetic neuropathy. The passage simply does not mention the cGMP-PDE5 mechanism of action. To the contrary, the passage emphasizes the mechanism of action as being "their blood sugar level-depressing activity" and thus teaches away from the cGMP PDE5 mechanism or at least results in confusion as to what the reference discloses.

Further with regard to the second passage, the Final Rejection provides no motivation to modify the disclosure (col. 35, lines 22-36) of the reference, from a disclosure of certain benzimidazole derivatives as suggested for preventing and treating a plethora of about two dozen disease/conditions "based on their blood sugar level-depressing activity", to a disclosure of the use of cGMP PDE5 inhibitors for the treatment of diabetic neuropathy. In fact, since the passage directly links the treatment of the many disease/conditions (including diabetic neuropathy) with the blood sugar level-depressing mechanism, it clearly implies that such treatment is not a result of the cGMP PDE5 mechanism.

In the third passage (col. 35, lines 22-25 and lines 36-55) certain benzimidazole derivatives are suggested for preventing and treating about three dozen disease/conditions. Importantly, the diseases are stated to be treated based upon a variety of different mechanism of actions of the compounds. The list of mechanisms of action is at least six (it is clear that combinations of the mechanisms of actions is contemplated and this would raise the number of mechanisms of action to around 50; it is also clear that other isoforms of cGMP-PDE besides PDE-V inhibitors are also contemplated and this would raise the number of mechanisms of action substantially further). There is simply no motivation to select the combination of

disease/condition (i.e., diabetic neuropathy) and mechanism of action (i.e., cGMP-PDE-V inhibition) from the combined list of approx. three dozen disease/conditions and approx. 50 mechanism(s) of action. Nor is there any reasonable expectation of success that the match-up of any particular disease/condition and mechanism of action is relevant or appropriate. For example, it is clear in col. 35 lines 21-55 that Yamasaki et al. does not disclose that smooth muscle relaxing activity mediates all the disease/conditions listed in col. 35, lines 36-51 (e.g., diabetic cataract).

Further, with regard to the third passage, the rejection provides no motivation to modify the disclosure (col. 35, lines 22-25 and lines 36-55) of the reference from a disclosure of certain benzimidazole derivatives as suggested for preventing and treating a plethora of disease/conditions based on several different mechanism of actions (without tying together each disease/condition and a particular mechanism of action) to a disclosure of the use of certain inhibitors for the treatment of diabetic neuropathy

The Examiner has taken a different position with regards to this specific passage in the Final Rejection (page 3)

> "Yamasaki et al. not only expressly teaches the treatment of diabetic neuropathy at col. 35, lines 49-50, but further expressly teach that such neuropathy may be treated "based on their [the disclosed benzimidazole compounds] cGMP-PDE (especially PDE-V)-inhibiting activity, smooth muscle relaxing activity, bronchodilating activity, vasodilating activity, smooth muscle cell suppressing activity and antiallergic activity", (emphasis added; col. 35, lines 52-55). This teaching is clear, exact and unequivocally speaks to the contrary of Appellants' opinion."

Appellants submit that the Examiner's interpretation is not unequivocally clear. Quite simply the Examiner has taken a quote out of context. First, the Examiner has utilized hindsight in selecting this passage in isolation without assessment of it in combination with the other passages that are discussed herein . Then the Examiner has paraphrased a sentence by selecting one particular disease from among many. This is clearly the impermissible use of hindsight. Then the Examiner has combined the preselected disease treatment with a specific quotation of several disease mechanisms (e.g., antiallergic activity). Further, elsewhere in the Final Rejection in referring to this passage the Examiner selects the cGMP PDE5 mechanism of action from among several.

In addition, there is simply no motivation to select the combination of disease/condition (i.e., diabetic neuropathy) and mechanism of action (i.e., cGMP-PDE-V inhibition) from the combined list of approx. three dozen disease/conditions and at least approx. 50 mechanism(s) of action. Nor is there any reasonable expectation of success that the match-up of any particular disease/condition and mechanism of action is relevant, appropriate or would provide a reasonable expectation of success. Any relationship between cGMP PDE-V mechanism and diabetic neuropathy that exists from the existence of both phrases in the same patent document is simply at best an invitation to explore many lines of research and insufficient to provide a *prima facie* case. This is particularly true when all the passages are taken as a whole (which they must be) in light of the confusion caused by the contradictory/uncertain passages discussed herein. Accordingly, one would not have been motivated to utilize any compound having the ability to inhibit cGMP-PDE-V for the treatment of diabetic neuropathy.

In the fourth passage, (col. 164, lines 65-67-col.165, lines 1-26) certain benzimidazole derivatives having blood sugar level-depressing activity or cGMP PDE5 activity are suggested for preventing and treating about five dozen disease/conditions. While one of the disease/conditions listed is diabetic neuropathy it is more likely that the diabetic neuropathy disease/condition would be linked with the blood sugar level-depressing activity given the well known connection between blood sugar level-depressing activity and diabetic type conditions. In any event, it is certainly unclear whether it is the blood sugar level-depressing activity or the cGMP PDE5 activity that is linked with any of the several dozen disease/conditions listed including diabetic neuropathy.

In addition, the Final Rejection does not provide motivation to modify the disclosure of the fourth reference (col. 164, lines 65-67-col.165, lines 1-26) from a disclosure of a multitude of uses (including diabetic neuropathy) for certain benzimidazole derivatives having blood sugar level-depressing activity or cGMP PDE5 activity to the use of cGMP PDE5 inhibitors for the treatment of diabetic neuropathy.

Appellants submit that these four passages <u>taken as a whole</u> lack a clarity of description and science that results in confusion regarding what is disclosed/intended. Further the reference actually suggests in some passages that diabetic neuropathy is treated through blood sugar lowering activity not a cGMP PDE5 mechanism (the opposite of that stated by the Examiner). At best this leads to a suggestion for further research which is a classic "obvious to

try" case discussed further below in section F.

E. RELIANCE ON ANTICIPATION LAW IS MISPLACED IN THIS OBVIOUSNESS DETERMINATION

The Final Rejection (page 5) states Appellants apparently believe that in some way the comprehensiveness of the disclosure of the patentees distracts from the teaching of a specifically disclosed disease/condition quoting MPEP § 2131.02

> "A Reference That Clearly Names The Claimed Species Anticipates The Claim No Matter How Many Other Species Are Named", (emphasis added) where it is set forth :"A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) ..... *In re Sivaramakrishnan*, 213 USPQ 441 (CCPA 1982)".

The reliance on the MPEP and case law related to anticipation is clearly wrong as Appellants have not been rejected under 35 U.S.C. 102. The gap in Yamasaki et al.'s teachings and the obviousness rejection cannot be bridged by reliance on anticipation law. First, MPEP § 2131.02 addresses anticipation and not obviousness. Second, *Ex parte A* involved a situation where the cited reference affirmatively taught a limited group of compounds. The issue in *Ex parte A* was whether the listing of compounds anticipated an individual compound and that holding had nothing to do with obviousness. Restated the Examiner improperly relied on *Ex Parte A* in an obviousness context. The anticipation holding of *Ex Parte A* is not relevant to the current obviousness rejection. For analogous reasons, *In Re Sivaramakrishnan* does not complete the deficiencies of *Ex Parte A*.

F. THE EXAMINER'S REJECTION IS CONTRARY TO THE LAW OF OBVIOUSNESS- AT BEST THIS IS A CLASSIC CASE OF "OBVIOUS TO TRY"

Appellants further submit that, at best, the references relied on by the Examiner make Appellants' invention no more than "obvious to try", but that "obvious to try" is not the proper standard for patentability. Further, the Examiner has not made out a *prima facie* case of obviousness because, *inter alia* (1) the references provide insufficient motivation or suggestion that a PDE-V inhibitor could or should be tried in the treatment of diabetic neuropathy and (2) even allowing, *arguendo*, that such suggestion or motivation were found in these references,

the references provide no reasonable expectation of success particularly in combination with an alpha 2 delta ligand.

The law is emphatic that "obvious to try" is not the test of obviousness under 35 U.S.C. §103. In American Hospital supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984) the Federal Circuit explained the proper test:

> The consistent criterion for determination of obviousness is whether the prior art **would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Clir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

As explained fully below, the art cited by the Examiner, at most, makes it no more than perhaps obvious to explore an area of research, and this is one of the classic hallmarks of an "obvious to try" rejection:

> "The admonition that 'obvious to try' is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful...**In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."**

In re O'Farrell, 7 USPQ2d 1673, at 1681, (Fed. Cir. 1988), emphasis supplied.

For example, Yamasaki et al. (col. 35, lines 22-25 and lines 36-55) is simply a classic invitation to experiment to determine which disease/condition should be linked with a particular mechanism of action (as explained more fully herein) . At best, this is an invitation to "explore a new technology or general approach that seemed to be a promising field of experimentation,

where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."

The Examiner states in the Final Rejection (page 6) that he agrees with Appellants that 'obvious to try' is not the standard for obviousness and he further states that what is claimed is what would have been "obvious to do" and the rejection is not based on what is "obvious to try". The Examiner states that the treatment of diabetic neuropathy, as well as any other of the clearly named diseases/conditions would have been obvious because such diseases/conditions are clearly named by the patentees.

Again, while such diseases are disclosed the treatment of such diseases are not linked to cGMP PDE5 inhibition. It is simply not clear which mechanism of action (more than one could also be required) is linked with which disease, particularly in light of the confusing/contradictory descriptive passages in Yamasaki, et al.. One skilled in the art would use the mechanism of action and disease/condition lists as a starting point for research.

The Examiner appears to state several times that the benzimidazole compounds are cGMP PDE5 inhibitors and that they are useful for the treatment of diabetic neuropathy, and accordingly all cGMP PDE5 inhibitors are useful for the treatment of diabetic neuropathy. If the only mechanism of action listed was cGMP PDE5 and the only disease listed was diabetic neuropathy that may be true. However, the reference simply does not state that. All of the listed disease/conditions are not mediated by all the mechanisms (if that is the interpretation urged than the reference's credibility as a scientific document degrades and, with that degradation, <u>any</u> motivation or likelihood of success disappears). The treatment of diabetic neuropathy by the benzimidazole compounds could be mediated by some other listed mechanism of action(s) (e.g., smooth muscle cell suppressing activity or yet another cGMP PDE isoform). Thus, the reference never directly links the two i.e., cGMP PDE5 inhibition and diabetic neuropathy. Any proposed connection in Yamasaki et al. between cGMP PDE5 and diabetic neuropathy is further confounded and confused by the <u>first</u> statement on col. 35, line 35-36 that diabetic neuropathy treatment and other diabetic related indications are actually treated based on their <u>blood sugar level-depressing activity (not their cGMP PDE5 activity)</u>. Thus, the same reference states that diabetic neuropathy (in addition to a variety of other disease/conditions) is treated based on blood sugar level-depressing activity of the compounds in addition to, or possibly as an alternative to one or more other various mechanisms of action.

This appears to teach away from the treatment of diabetic neuropathy by cGMP PDE5 activity. Further, these statements in combination create a level of description and scientific confusion that at best suggests that more research is further needed or that the reference's credibility as a scientific document is so degraded that any motivation or likelihood of success disappears.

Further, even if the art is, *arguendo*, viewed as providing a suggestion, it clearly provides no reasonable expectation or likelihood of success. Thus, even if an argument could be made that the art provides a suggestion to explore the use of PDE5 inhibitors to treat diabetic neuropathy, this amounts to no more than an invitation to experiment, i.e., to perhaps making and testing PDE5 inhibitors more obvious to try, which again is manifestly not the proper standard for patentability. O'Farrell, supra. And yet the Examiner's position is still insufficient for an obviousness finding as the cGMP PDE5 compound must still be combined with pregabalin or gabapentin.

The Final Rejection references In Re Kerkhoven, 205 USPQ 1069 (CCPA 1980). Even assuming arguendo use of the two agents for the same purpose, which Applicant does not concede (see explanation above), the applicable case law specifically addressing the combination of two agents, each known individually for the same purposes fully supports the Examiner's failure to carry his burden of establishing *prima facie* obviousness. Thus, In re Geiger, 2 USPQ2d 1276 (Fed. Cir. 1987) governs here and not, as the Examiner contends, the older decision of In re Kerkoven, 205 USPQ 1069 (CCPA 1980) (see also MPEP 2144.06). As the Federal Circuit held in Geiger, "at best" the combination proposed by the Examiner evidenced a general incentive to "try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 USC § 103." (2 USPQ2d at 1278). In Geiger, the components of the claim were broadly used in water treatment, albeit different aspects of water treatment: corrosion prevention and scale prevention. Appellant's claimed invention is even more unobvious than Geiger since an alpha 2 delta compound ligand and a PDE V inhibitor function by two entirely different mechanisms (i.e., a cGMP PDE5 mechanism and an alpha 2 delta mechanism; this further confounds the ability to guess at their effects if combined). But it is clear from In re Geiger that even if the compounds were broadly used for the same purpose that only evidences a general incentive to try various combinations.

The Final Rejection (page 7) states that unlike in Geiger, the reference was not as specifically detailed as Yamasaki et al. The Final Rejection also states that short of

anticipating the use of the claimed PDE5 inhibitor, it is believed that the clear teaching of Yamasaki et al. provides the reasonable expectation and motivation to employ other compounds possessing the same function and to reasonably expect the same results to occur as in Yamasaki et al. The Final Rejection refers to the MPEP at § 2144.06 where "Art Recognized Equivalence for the Same Purpose" is discussed, and in particular, the "substituting equivalents known for the same purpose".

Appellants urge that, as expansively detailed above in section D, Yamasaki does not "specifically detail" the use of PDE5 inhibitors for treating diabetic neuropathy nor is the alleged use "clear". In addition, in light of Appellants detailed analysis of the relevant passages in Yamasaki and the further need for combination with gabapentin and pregabalin the Examiner's argument is analogous to that which was overturned in In Re Geiger as detailed in the MPEP.

> "Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating, cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. 103, to employ these components in combination for their known functions and to optimize the amount of each additive...Appellant argues...hindsight reconstruction or at best..."obvious to try"... We agree with appellant."
>
> MPEP § 2144.01

G. LACK OF REASONABLE EXPECTATION OF SUCCESS FROM COMBINATION OF TWO DRUGS HAVING DIFFERENT MECHANISMS OF ACTION

The Examiner in the Final Rejection (page 8) erroneously stated that "two or more compounds, used together, may have different mechanisms of action [resulting in a drug-drug interaction] is not very impressive of an argument against such use because if this were true, than it would have to be the case that no two or more drugs could be used in combination with each other unless they each possessed the same mechanism of action." Appellants have never stated (nor is it true) that all drugs having different mechanisms of action will have deleterious drug-drug interactions. But it is true that such drug combinations may have drug-drug interactions and it is exactly the unpredictability of such drug-drug interactions that is an important aspect of the lack of a reasonable expectation of success of Appellants' drug combination.

The rejection states that it would be obvious to employ either gabapentin or pregabalin in combination with a cGMP inhibitor. This oversimplifies the combination of pharmaceutical agents. The Examiner appears to proceed from the assumption that it is a common technique in the pharmaceutical field to formulate ingredients, which have conventionally been contained in separate tablets, into a single formulation. This appears to take it for granted that any two known separate pharmaceutical agents can or should be combined. Again, this vastly oversimplifies the position. Counterbalanced against the possibility of improved patient compliance, there are many reasons why those skilled in the art would not pursue a particular combination. For example, there have been many examples of combination agents that have exhibited poor performance and even dangerous side effects. One example is the diet drug "PHEN-PHEN" (a combination of phentermine and fenfluramine) which resulted in damage to heart valves and was removed from the market. In addition, virtually all approved pharmaceutical agents have "drug-drug" interactions that restrict their use in combination with other pharmaceutical agents.

In the 1990s, it had become widely recognized that drug interactions/combinations can result in unexpected effects. For example, there is a chapter in a widely used standard text, Remington: The Science and Practice of Pharmacy, 19th Edition, Chapter 105 (Drug Interactions, by DA Hussar), pages 1822 – 1836, edited by AR Gennaro, Mack Publishing Co. Easton, 1995, that outlines the state of knowledge at that time. Physicians and regulators had already at that time been sensitized to drug interaction issues by several highly publicized tragedies caused by drug interactions. These interactions occur at different levels one of them being pharmacology and can impact both safety and efficacy of the interacting agents.

A pharmacological interaction is the result of combining drugs (such as gabapentin and a PDE5 inhibitor), which act upon different factors. Accordingly, they may interact in a manner detrimental to the treatment of disease.

Restated, agents which act upon different factors may not interact in a manner beneficial to the treatment of disease. Diabetic neuropathy and its progression are the result of a complex series of interconnecting factors which continue to be studied by the medical community. Gabapentin interacts with one factor (alpha 2 delta) while a cGMP PDE5 inhibitor acts upon a different and separate factor i.e., cGMP PDE5. In the complex system of factors that combine to produce diabetic neuropathy and contribute to its progression, the combination

of an agent useful in acting against one factor could just as easily cancel out the usefulness of a second agent useful in acting against a separate factor (assuming arguendo the reference teaches this).

In the Final Rejection the Examiner states (page 8):

> "The fact that different drugs are involved in the presently claimed subject matter is not seen as confounding. In the primary reference, Yamasaki et al. makes use of an astronomical number of "different" compounds, i.e., benzimidazole derivatives which are, in relation to each other, "different", and does so successfully. Also, it is not seen that the alpha 2 delta compound ligand (i.e., gabapentin or pregablin) and the PDE5 inhibitors have different functions. They were both well known in the art to function as treatments for diabetic neuropathies. Finally, that two more compounds, used together, may have different mechanisms of action is not very impressive of an argument against such use because if this were true, than it would have to be the case that no two or more drugs could be used in combination with each other unless they each possessed the same mechanism of action."

Appellants strongly submit that the fact that Yamasaki et al. makes use of an astronomical number of compounds that are in relation to each other "different" is irrelevant. First, the Examiner does not state that the compounds are used in combination with each other as stated in Appellants claims. Second, the Examiner is wrong in stating that the alpha 2 delta ligands and cGMP PDE5 inhibitors have common functions. The Examiner's analogy to the Yamasaki et al. compounds is an incorrect analogy since they are disclosed as sharing common mechanisms of action (although it is not at all clear what those are from the internal contradictions of Yamasaki et al.) in contrast to Appellants claimed combination which have two different mechanisms of action. This is a critical point with regard to drug-drug interactions in that the Examiner is confusing disease treatment with mechanism of action. Fundamentally, an alpha 2 delta ligand and a cGMP PDE5 inhibitor interact with two different enzyme targets and, accordingly, interact with two different enzyme pathways. This can result in an agent useful in acting against one factor (enzyme target), canceling out the usefulness of a second agent useful in acting against a separate factor (enzyme target). Further, the Examiner's contention that the well recognized concept of drug-drug interactions is not real, "because drug combinations would not be useful unless they each possessed the same mechanism of action" is simply wrong. Drugs having different mechanisms of action may have a drug-drug

interaction or they may not. Appellants have never stated (nor is it true) that all drugs having different mechanisms of action will have deleterious drug-drug interactions. But it is true that such drug combinations may have drug-drug interactions and it is the unpredictability of such drug-drug interactions that is an important part of the lack of a reasonable expectation of success of Appellants drug combination.

This lack of a reasonable expectation of success is reinforced and made clearer by further remarks in the Final Rejection. The Final Rejection states that "[T]hat is, the possibility that the presently claimed combination of actives could have dangerous effects is not sufficient. The Examiner could equally take the position, and support such a position with a significant number of examples, in both the patent and non-patent literature, where drug combinations are taught and which have a favorable benefit-to-risk profile."(Final Rejection page 10) Appellants strongly submit that the Examiner has in these statements admitted the lack of reasonable expectation of success. Appellants submit that the Examiner has admitted that in this instance there may "possibly" be a problem with combining the drugs or there may "possibly not" be a problem–the outcome is equally unclear. This is a clear example of the lack of a reasonable expectation of success.

The Examiner also stated that "hypothetical teachings away simply do not serve the place of an actual contraindication to a particular combination of active agents". Appellants maintain that the burden is not on Appellants to demonstrate an actual contraindication to the particular combination of active agents. This is a standard that well exceeds the "lack of reasonable expectation of success" standard. Appellants have raised a sufficient question regarding the expectation of success as admitted by the Examiner when he noted that he could equally take a contrary position and support it with examples. Restated, Appellants do not have the burden of proving a drug-drug interaction rather their burden is to raise sufficient doubts of the reasonable expectation of success In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). It bears emphasizing that the legal standard is "reasonable expectation of success", and not "wish for success", "hope for success", or "possibility of success".

Appellants have met the burden and also have made note of the skill in the art's awareness of such problems by referring to the citation (the widely used standard text, Remington: The Science and Practice of Pharmacy, 19th Edition, Chapter 105 (Drug Interactions, by DA Hussar), pages 1822 – 1836, edited by AR Gennaro, Mack Publishing Co.

Easton, 1995) and an exemplary drug-drug interaction. Accordingly, the Examiner failed to establish a reasonable expectation of success.

Appellants also submit that claims 21 and 32 are unobvious since they are directed to a combination composition comprising the specific cGMP PDE5 inhibitor sildenafil (or its pharmaceutically acceptable salts; hereinafter sildenafil) and gabapentin or pregabalin. There is nothing in the art cited (Ellis et al.) to motivate one to select the particular compound sildenafil from among all the cGMP PDE5 inhibitors disclosed. In analogous genus-species cases, the Federal Circuit has repeatedly decided against prima facie obviousness, In re Baird, 16 F.3d 380, (Fed. Cir. 1994); In re Jones 958 F.2d 347 (Fed. Cir. 1992). Thus, In re Jones, 21 held no prima facie obviousness even though the prior art generically taught Applicants' claimed substituted amine salt of dicamba and the specific salt moiety was known for other acids.

Appellants submit that (WO 94/28902), Singh (WO 98/03167), Bueno et al. (U.S. Patent No. 6,127,418) and Stedman's Medical Dictionary do not overcome the deficiencies of the previously described references.

In summary, Appellants respectfully request that this application be passed to issue. There is nothing in Yamasaki et al. (or the other cited art) that motivated one skilled in the art to select diabetic neuropathy from among the many disease/conditions listed or to select the cGMP PDE5 mechanism. There is clearly nothing to directly link the selected diabetic neuropathy with the selected cGMP PDE5 mechanism. Further still, there is nothing to suggest the combination of the selected cGMP PDE5 inhibitor with the further selected specific gabapentin or pregabalin since they have different mechanisms of action, or were that combination made, that there would be a reasonable expectation of success. At least all of these selection and combination steps must occur for there to be a *prima facie* case of obviousness and the quality and quantity of selection and combination steps presents a clear case of the impermissible use of hindsight. Further still, Appellants have raised a sufficient doubt as to the reasonable expectation of success, at least because of the confusion due to the conflicting Yamasaki et al. statements and as a result of the possible drug-drug interactions.

CONCLUSION

For the foregoing reasons Appellant requests that the rejections of claims 17-34 under 35 U.S.C. §103(a) be reversed.

Respectfully Submitted By:

10/19/06
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APPENDIX A

CLAIMS ON APPEAL

1-16. (Cancelled)

17. (Previously Presented) A combination comprising a therapeutically effective amount of a cGMP inhibitor and a therapeutically effective amount of pregabalin or gabapentin.

18. (Previously Presented) A pharmaceutical composition comprising:

a therapeutically effective amount of a first compound said compound being a cGMP inhibitor;

a therapeutically effective amount of a second compound said second compound being pregabalin or gabapentin; and

a pharmaceutically acceptable excipient, diluent or carrier.

19. (Previously Presented) The pharmaceutical composition as recited in claim 18 wherein the inhibitor has an IC50 at less than 100 nanomolar.

20. (Previously Presented) The pharmaceutical composition as recited in claim 19 wherein the inhibitor has a selectivity ratio in excess of 100.

21. (Previously Presented) The pharmaceutical composition as recited in claim 18 wherein the inhibitor is sildenafil, or pharmaceutically acceptable salts thereof.

22. (Previously Presented) The pharmaceutical composition as recited in claim 18 wherein said second compound comprises a therapeutically effective amount of pregabalin.

23. (Previously Presented) The pharmaceutical composition as recited in claim 18 wherein said second compound comprises a therapeutically effective amount of gabapentin.

24. (Previously Presented) The pharmaceutical composition as recited in claim 22 or 23 wherein the inhibitor has an IC50 at less than 100 nanomolar.

25. (Previously Presented) The pharmaceutical composition as recited in claim 22 or 23 wherein the inhibitor has a selectivity ratio in excess of 100.

26. (Previously Presented) The pharmaceutical composition as recited in claim 22 or 23 wherein the inhibitor is sildenafil, or pharmaceutically acceptable salts thereof.

27. (Previously Presented) A method of treating neuropathy in a patient suffering therefrom which comprises administering a patient in need of therapy thereof a therapeutically effective amount of a combination of a cGMP inhibitor and pregabalin or gabapentin.

28. (Previously Presented) A method as recited in claim 27 wherein the neuropathy is diabetic polyneuropathy.

29. (Previously Presented) A method as recited in claim 27 or 28 wherein the inhibitor is administered orally.

30. (Previously Presented) A method as recited to claim 29 wherein the inhibitor has an IC50 at less than 100 nanomolar.

31. (Previously Presented) A method as recited in claim 29 wherein the inhibitor has a selectivity ratio in excess of 100.

32. (Previously Presented) A method as recited in claim 29 wherein the inhibitor is sildenafil, or pharmaceutically acceptable salts thereof.

33. (Previously Presented) A method according to claim 29 wherein pregabalin is administered.

34. (Previously Presented) A method according to claim 29 wherein gabapentin is administered.

APPENDIX B

EVIDENCE APPENDIX

COPIES OF CITED REFERENCES PROVIDED HEREWITH

Yamasaki et al. (U.S. Patent NO. 6,166,219)

Ellis et al. (WO 94/28902)

Singh (WO 98/03167)

Bueno et al. (U.S. Patent No. 6,127,418)

Stedman's Medical Dictionary